UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,098	06/24/2004	Anne D. Frame	083622/00003	7662

25223 7590 04/14/2009

WHITEFORD, TAYLOR & PRESTON, LLP
ATTN: GREGORY M STONE
SEVEN SAINT PAUL STREET
BALTIMORE, MD 21202-1626

EXAMINER	
LEITH, PATRICIA A	

ART UNIT	PAPER NUMBER
1655	

MAIL DATE	DELIVERY MODE
04/14/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,098	FRAME, ANNE D.	
	Examiner	Art Unit	
	Patricia Leith	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,26-32,34,35,40-49,56-59 and 62* is/are pending in the application.

4a) Of the above claim(s) *1-15,26-31,34,35 and 42-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32 and 40-41, 47-49, 56-59 and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/7/2009 has been entered.

Claims 1-15, 26-32, 34-35, 40-49, 56-59 and 62 are pending in the application.

Claims 1-15, 26-31, 34-35 and 42-46 remain withdrawn from the merits as being directed toward a non-elected invention.

Claims 32 and 40-41, 47-49, 56-59 and 62 were examined on their merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a previous Office Action.

Mammea americana may be referred to herein as *Mammea americana*, *M.americana* or 'MA.'

Applicant's amendments overcome the previous rejections set forth under 35 USC 112 First and Second paragraphs.

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 32 and 40-41, 48-49, 56-59 and 62 remain rejected, as necessitated by Applicant's most recent amendments to the claims on 1/7/2009 under 35 U.S.C. 103(a) as being unpatentable over Frame et al. :*Antimicrobial Phytochemicals*, P.R. Health Sci. J., (1998) (as cited in the IDS submitted by Applicant on 6/24/2004) in view of McMurry (1992) in view of Greenspan et al. (1996).

Frame et al. (1998) taught that the ethanolic extract of *Mammea americana* leaves displayed inhibitory activity against *Mycobacterium tuberculosis*, demonstrated via screening for anti-Mycobacterium activity using the Buer-Kirby agar diffusion method (see entire reference, especially 'Materials and Methods', pp. 244-247, Tables 1 and 2, p. 247). Frame et al. indicated that "...efforts are directed at purifying and characterizing the physical and chemical properties of the promising anti-mycobacteriological agents discovered in this study." (p. 251, under 'Discussion').

Frame et al. did not teach chromatographic separation of the endogenous components of the *M.americana* ethanol extract (including elution) to obtain one fraction or more than one fraction , wherein the composition comprised stigmastan-3,5,-diene, friedelin and additionally cyclododecane or acetic acid.

The use of chromatography in science is ubiquitous. Chromatography media are conventionally used to separate compounds in crude extract preparations based upon solubility, ionic charge and size for example (see McMurray pp. 413-414).

Greenspan et al. (1996) disclosed a method for extracting leaves and seeds of *Mammea americana* to produce an insecticidal composition against larvae of *Diabrotica virgifera* v. (see entire reference). Specifically, Greenspan et al. lyophilized the seeds and leaves (respectively) and carried out individual hexane (organic solvent) extractions of the lyophilized seeds and leaves followed by thin layer chromatography to elucidate the compounds endogenous therein (see 'Materials and Methods', pp. 237-238).

Hence, it was known in the art that an alcoholic extract of *Mammea americana* inhibited the growth of *Mycobacterium tuberculosis in-vitro* via assaying for mycobacterial activity; specifically assaying for *Mycobacterium tuburculosis* activity was described by Frame et al. Clearly relayed by Frame et al. was the advantageous nature of purifying compounds responsible for this anti-mycobacterial effect. The next natural step in purification of compounds from the crude MA extract would be chromatographic separation. This step is not considered unique or inventive in that the use of chromatography, again, is ubiquitous in the art of science; widely used in order to successfully separate and elucidate endogenous phytochemicals. Greenspan et al. themselves clearly used chromatography to separate endogenous chemicals in their

MA extract. Accordingly, motivation was present in the art to further purify an active fraction or to identify and isolate active ingredients present in the ethanolic extract of *Mammea americana* to use on Mycobacterium as was plainly stated by Frame et al. Greenspan et al. for example, used TLC (thin layer chromatography) to separate endogenous compounds in an MA extract. Although Greenspan et al. did not specifically teach elution of the extract from a chromatographic system, this is clearly because Greenspan et al. used TLC and not column chromatography to elucidate the MA extracts. One of ordinary skill in the art would have had a reasonable expectation of success in carrying out the claimed process in that the ordinary artisan would have been well-aware that column chromatography systems were well-known and well-utilized at the time the invention was made and that column chromatography, which incorporates eluting compounds from the column containing stationary medium was well-known (again, see McMurray). Where claim 59 states 'selecting or having pre-selected a fraction having antimicrobial activity for elution' is very broad and is covered by the combination of references. To reiterate, it would have been obvious to submit the extract of Frame et al. to chromatography techniques to elucidate anti-bacterial compounds therein. It was known that the alcoholic extract had anti-microbial activity and, again, lacking any substantive characteristics regarding the chromatography process in the claims, the entire extract may be eluted via the method of claim 59. Further, no matter what chromatography media is used, a fraction eluting from a chromatographic separation system containing the ethanol extract of MA will contain an active fraction. 'Selecting or having pre-selected a fraction having antimicrobial activity'

is simply a mental step in the process and does not significantly change the process as claimed. Applicant is adding steps into the method which are conventional steps in purifying components of crude mixtures; such steps being well-known in the art and utilized in purification protocols.

There is no step in the methods as claimed which indicates what type of column media was used (stationary phase), what fractions were collected or what organic solvent was used; in other words, there is no series of steps present in the claimed invention which creates a non-obvious variation of what the prior art as combined plainly renders *prima facie* obvious. While the prior art did not specifically teach placing the crude MA extract over a column, but instead, chose to elucidate their extract via TLC, it is deemed that the ordinary artisan would have clearly recognized the advantage of using column chromatography for processing large batches of extract in order to manufacture and standardize the extract.

Additionally, considering the lack of specifics in the claims regarding specific chromatography media, elution type (solvent), elution times, number and volumes of fractions collected, the composition eluted from the method of the claims may be the same composition which was placed in (or on/over) the chromatography apparatus. The claim is so extensively broad, that it reads on eluting the entirety of the original extract which was placed in (or on) the chromatography media into one vessel. Since Frame et al. already taught that the ethanolic extract of MA leaves possessed anti-

bacterial activity, the 'fraction' or 'composition' as referred to by claim 32 which is 'administered' to a bacteria may be the same 'composition' which was assessed for anti-bacterial activity by Frame et al.

Claims 40-41 are directed to wherein the composition comprises stigmastan-3-5,-diene, friedelin for example. Claim 57 is directed toward wherein the composition comprises a terpene a caryophylene and a cyclododecane. Applicant's specification, in Table 2 identifies compounds in the methylene chloride extract as well as the ethanol extract of MA leaf. Table 5 of Applicant's specification displays certain fractions from an extract of MA, however, the specification does not definitively state from which extract these fractions were obtained. First, it must be pointed out that neither cobaltocene-octomet, friedelin nor stigmastan-3,5-diene were identified by gas chromatography in either of the crude methylene chloride or the ethanol extracts of MA leaf and are therefore not represented by Table 2. The first time these compounds were identified were after fractionation of the crude MA extract and analyzed by GC/MS (according to Table 5). Upon careful consideration, it can be deduced that the fractions of MA displayed in this table originate from the ethanolic extract. This deduction arises because acetic acid was identified in HPLC fraction 2 of the MA extract according to Table 5; however, *acetic acid was only identified in the ethanol extract of MA and not in the methylene chloride extract of MA*. Clearly, if acetic acid were in the methylene chloride extract of MA the GC/MS would have detected it. The other compounds

identified in the fractions as displayed in Table 5 were common to both the methylene chloride as well as the ethanol extract. Hence, it can be said that the ethanol extract of MA leaf contains friedelin, stigmastan-3,5-diene, cobaltocene-octamethyl, cyclodecene, caryophylene and acetic acid. Further, it must also be noted that Applicant states that the HPLC column was eluted with a polar solvent: dilute phosphoric acid in methanol. This elution system would not be appropriate for use with a methylene chloride extract which is non-polar (see p. 22, Specification). And again, because the claims are so broad that they read on elution of the entirety of the extract which is placed in (or on, or over) a chromatographic media, it is deemed that the product obtained from the claimed invention is equivalent to the alcoholic extracts of MA as disclosed by Frame et al. as well as Greenspan et al. Hence, the combination of references makes obvious administration of a 'fraction' as referred to by Applicant's claims, which is analogous to the ethanolic extract of Frame et al., to bacteria.

Applicant has amended claim 32 to include wherein a fraction is eluted which contains stigmastan-3,5-diene and wherein the method comprises assaying the fraction to ascertain the fraction has antibacterial activity.

While the prior art did not expressly recognize that stangastan-3,5, diene was present in the methanolic extract of MA leaves, with regard to patentability of the method, the Examiner must assess the differences between the method as currently claimed and the methods as cited in the prior art. It has already been determined that

stigmastan, 3, 5 diene is present in the methanol extract of MA leaves as determined by gas spectrophotometry carried out by Applicant and documented in the Specification. The method remains very broad and may be directed toward elution of one single fraction off of a chromatography column; whereby said fraction happens to include stigmastan, 3, 5 diene. Again, the method is so broad as it can include the entirety of the methanol extract in the fraction. It would have been obvious to elute a fraction containing the entirety of the methanolic extract of MA leaves because this extract was shown to be antibacterial according to Frame et al. The discovery of trace constituents in this extract such as stigmastan, 3-5 diene is not deemed patentable absent an unexpected result; especially considering that Applicants did not test any fraction or isolated compound besides the fraction containing acetic acid, cobaltocene-octomet, stigmastan-3,5, diene, friedelin and terpene for antibacterial activity. The method claims, amended to describe that the fraction consists of this particular fraction: acetic acid, cobaltocene-octomet, stigmastan-3,5, diene, friedelin and terpene, may be allowable, however, Applicants are not now claiming this particular fraction and the compounds present in the 'fraction' as currently claimed are all intrinsic to the methanolic extract disclosed by Frame et al. Clearly, one of ordinary skill in the art would have been motivated to use the methanol extract of Frame et al. for anti-bacterial purposes because Frame et al. clearly demonstrated that this extract possessed anti-bacterial properties. Subsequently, one of ordinary skill would have been motivated to assay the methanolic 'fraction' for antibacterial activity, independent upon minor

chemical constituents present in the fraction, because the methanolic extract (fraction) was already known to possess anti-bacterial ability.

As it has been clearly pointed out in previous Office actions, Applicant's methods are so broad as they read on one pass of a methanolic extract of MA leaves over a chromatographic separation column. The fraction may include the entirety of the initial methanolic extract of MA leaves; the same composition disclosed by Frame et al. The use of chromatography media is obvious as described in previous Office actions, and is not considered the inventive nature of Applicant's specification.

Claims 32 , 40-41, 47-49, 56-59 and 62 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Frame et al. (1998) in view of Greenspan et al. (1996) in view of McMurray (1992) in view of Habtemarium et al. (US 6,225,342) ***or*** Kanojia (US 4,046,882 A).

Claim 47 states wherein the organic solvent of claim 32 is specifically methylene chloride (also known as dichloromethane).

The teachings of Frame et al., Greenspan et al. and McMurray were discussed *supra*. It is reiterated that Greenspan incorporated hexane for extraction of *Mammea americana* leaves and seeds, however, did not specifically disclose use of methylene

chloride, nor did Greenspan et al. explicitly disclose that the extract was administered to a bacteria *per se*.

Interchanging non-polar solvents was routine, conventional practice in the herbal extract art. Methylene chloride, also known as dichloromethane, was also a well known non-polar solvent (extractant) used to extract plant materials. Both Habtemarium et al. (US 6,225,342) as well as Kanojia et al. disclose the use of hexane or methylene chloride for use as a non-polar solvent in extracting plant material. While it is accepted, of course that hexane (as disclosed by Greenspan et al.) and dichloromethane are not *exactly* the same solvent one of ordinary skill in the art would have had a reasonable expectation of substituting the hexane of Greenspan et al. with methylene chloride because both of these solvents were known non-polar solvents used for plant extraction and known to be interchangeable. "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton" *KSR* 127S. Ct. at 1742. Applicant has not demonstrated within the instant disclosure as filed that methylene chloride fairs any better than any other non-polar solvent which is known, and conventionally used in the prior art. Therefore, the Applicant's use of methylene chloride over hexane, without showing any unexpected results therefrom, is considered an obvious variation of the method already disclosed in the art by Greenspan et al.

While Greenspan et al. did not explicitly teach that their extract was administered to a bacteria, bacteria are ubiquitous. Claim 47 is broad enough to encompass

preparing a methylene chloride extract of MA and administering this extract to bacteria (again, it is reiterated that lacking specific steps in claim 32, the extract put in or on or over the chromatography media may be the same extract which is eluted from the chromatography media). Because, as explained *supra*, one of ordinary skill in the art would have been motivated to substitute a methylene chloride extract for the hexane extract of Greenspan et al. to produce an insecticidal composition, it is highly likely that administration of a methylene chloride extract to an insect would also be administration to a bacteria since bacteria are ubiquitous and reside most surfaces, and almost certainly on the surface of insects.

[If]... there are [a] finite number of identified, predictable solutions, [a] person of ordinary skill in art has good reason to pursue known options within his or her technical grasp, and if this leads to anticipated success, it is likely product of ordinary skill and common sense, not innovation *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 U.S. 2007.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant has amended claim 32 to include wherein a fraction is eluted which contains stigmastan-3,5-diene and wherein the method comprises assaying the fraction to ascertain the fraction has antibacterial activity.

While the prior art did not expressly recognize that stangastan-3,5, diene was present in the methanolic extract of MA leaves, with regard to patentability of the method, the Examiner must assess the differences between the method as currently claimed and the methods as cited in the prior art. It has already been determined that stigmastan, 3, 5 diene is present in the methanol extract of MA leaves as determined by gas spectrophotometry carried out by Applicant and documented in the Specification. The method remains very broad and may be directed toward elution of one single fraction off of a chromatography column; whereby said fraction happens to include stigmastan, 3, 5 diene. Again, the method is so broad as it can include the entirety of the methanol extract in the fraction. It would have been obvious to elute a fraction containing the entirety of the methanolic extract of MA leaves because this extract was shown to be antibacterial according to Frame et al. The discovery of trace constituents in this extract such as stigmastan, 3-5 diene is not deemed patentable absent an unexpected result; especially considering that Applicants did not test any fraction or isolated compound besides the fraction containing acetic acid, cobaltocene-octomet, stigmastan-3,5, diene, friedelin and terpene for antibacterial activity. The method claims, amended to describe that the fraction consists of this particular fraction: acetic acid, cobaltocene-octomet, stigmastan-3,5, diene, friedelin and terpene, may be

allowable, however, Applicants are not now claiming this particular fraction and the compounds present in the 'fraction' as currently claimed are all intrinsic to the methanolic extract disclosed by Frame et al. Clearly, one of ordinary skill in the art would have been motivated to use the methanol extract of Frame et al. for anti-bacterial purposes because Frame et al. clearly demonstrated that this extract possessed anti-bacterial properties. Subsequently, one of ordinary skill would have been motivated to assay the methanolic 'fraction' for antibacterial activity, independent upon minor chemical constituents present in the fraction, because the methanolic extract (fraction) was already known to possess anti-bacterial ability.

As it has been clearly pointed out in previous Office actions, Applicant's methods are so broad as they read on one pass of a methanolic extract of MA leaves over a chromatographic separation column. The fraction may include the entirety of the initial methanolic extract of MA leaves; the same composition disclosed by Frame et al. The use of chromatography media is obvious as described in previous Office actions, and is not considered the inventive nature of Applicant's specification.

Response to Arguments

Applicant's arguments pertain toward the assertion that because the claims have been amended to recite wherein stigmastan, 3, 5 diene (claim 32) and or stigmastan, 3,

5 diene or cobaltocene octamethyl (claim 59) appear in the method claims that these amendments overcome the prior art rejections. However, these amendments do not overcome the prior art for the reasons set forth *supra*.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia Leith whose telephone number is (571) 272-0968. The examiner can normally be reached on Monday - Friday 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on (571) 272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Patricia Leith
Primary Examiner
Art Unit 1655

/Patricia Leith/
Primary Examiner, Art Unit 1655